

REMARKS

Claims 1, 3-7, 9-16, 18-23, 26-27, and 38-42 are pending in the application. No new matter is added.

Claim rejection

35 U.S.C. § 112, first paragraph

Claims 1, 3-7, 9-16, 18-23, 26, 27 and 38-40 have been rejected for lack of enablement. The Examiner alleged that the screening methods of the instant claims would require undue experimentation to practice for one of ordinary skill in the art. The Examiner asserted that single gene association with disease syndromes are typically wrong, and that the methods of the instant claims will not produce meaningful results. Further, the Examiner suggests that there is a scope of enablement issue because the alleles claimed cannot be associated with every inflammatory disease nor can they be tied to most of the biomarkers claimed. Applicants respectfully disagree.

The invention is drawn to a method of screening for a substance that is likely to diminish a specific biological response in a subject with one of the genotypes listed. A specific biomarker is observed in a subject, who is then contacted with a test substance. The biomarker is again observed, after which the subject is administered an inducer and the biomarker is observed again. If the biomarker has changed, the method of the invention has shown that the test substance has been identified as a substance that is likely to prevent or diminish a specific biological response. The claims as pending do not require that any of the claimed alleles be linked to a disease, (although all of the claimed alleles are linked to inflammatory diseases) let alone be linked to every inflammatory disease. Nor do the claims require that each allele be linked to every biomarker imaginable.

The method of the invention is based on the finding of linkage disequilibrium among the claimed alleles.¹ Individuals with the 44112332 haplotype² are underproducers of IL-1 α and individuals with the 33221461 haplotype³ are overproducers of IL-1 α and IL-1 β . As shown throughout the specification, there is much evidence in the art that these cytokines are involved in a wide variety of inflammatory responses, as well as the proteins encoded by the genes that are

¹ See pages 12-13 of the instant specification.

² *Id.* at page 12.

³ *Id.* at page 13.

in linkage disequilibrium. Thus, alleles associated with these inflammatory disease associated haplotypes are useful for the screening of substances that effect biomarkers with inflammatory-disease associated phenotypes. The details supporting this argument are shown in greater detail, organized using the Wands factors, below.

The Wands factors may be used to determine whether a disclosure meets the enablement requirement.⁴ These factors are 1) the quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence of absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art and 8) the breadth of the claims.⁵ Each of these factors is analyzed in greater detail, below.

The Nature of the Invention

The claims are drawn to an invention in the biological and chemical arts, which have been characterized as unpredictable. However, while the biological and chemical arts are generally unpredictable, the nature of the claimed invention is not. The claims are drawn to a method to identify substances that affect a biological response in a subject with a certain genotype based upon the correlation of the effect on a biomarker after the administration of the substance with a subject with at least one of the claimed genotypes. The claimed genotypes have been associated with inflammatory diseases because the proteins they express are generally accepted in the art to be associated with inflammatory diseases, and because the alleles are associated by linkage disequilibrium with other alleles that form haplotypes with abnormal levels of immune proteins.

Prior to applying the method of the instant claims to a substance, it may be unpredictable whether or not the substance will have an effect on a biomarker. However, through use of the methods of the instant claims, this unpredictability is diminished. Thus, the nature of the invention is one in which unpredictability is reduced, not one characterized by inherent unpredictability.

⁴ In re Wands, 8 USPQ2d 1400 (CAFC 1988)

⁵ *Id.* at 1404.

The Breadth of the Claims

The Examiner alleged that the claims are extremely broad because they are open to any inflammatory disease or any biomarker. Applicants submit that the term “inflammatory disease” is used in only two ways in the claims as pending. The first way is in reference to an inflammatory disease related genotype. However, these genotypes are limited to the list of genotypes found in the claims as pending. The second way is in reference to an inflammatory disease associated phenotype that is changed in the biomarker. This term is limited because the phenotypes and biomarkers may only be in subjects with the inflammatory disease related genotypes recited in the claims. Thus, the term “inflammatory disease” cannot be interpreted broadly

Quantity of Experimentation

The Examiner alleged, on pages 5-6 of the Office Action, that the quantity of experimentation in this area is immense. That to validate the association of a single allele with a single biomarker or disease would take years of study with hundreds of patients. Further, that because the instant claims are drawn to twenty-one alleles the amount of experimentation involved would require, “more effort than is expended in the entire NIH budget.”⁶

Applicants submit that no experimentation is necessary in order to practice the invention of the pending claims. The pending claims are drawn to methods of identifying compounds that are likely to prevent or diminish a specific biological response in subjects with certain genotypes, by testing to see whether these compounds effect an inflammatory disease associated phenotype in the subjects. The method of the pending claim is a method of research, but it requires no additional experimentation for one of ordinary skill in the art to practice the invention.

The Examiner asserted in page 6 of the Office Action that Wacholder *et al.* J. Natl. Cancer Institute 96(6):434-442 (2004) (“Wacholder”) teaches that the association of mutation studies with larger sized studies creates greater statistical power. The Examiner suggests that this supports that the methods of the instant claims require hundreds or thousands of patient samples in order to be practiced. The methods of the invention carry no such requirement.

⁶ See page 6 of the Office Action.

Wacholder teaches that a greater number of experimental results leads to a reduction in false positive findings.⁷ However, Wacholder teaches only about the correlation between genotype and disease state not between genotype and specific biological response, as specified in the instant claims. As Wacholder teaches, diseases like cancer are complex,⁸ and correlations between disease state and genetic variants have a significant risk of false positives. However, the teachings of Wacholder do not suggest that the methods of the invention require undue experimentation to generate meaningful results. First, the screening method of the instant invention does not encompass the correlation of disease states with genotype, but only inflammatory disease related phenotypes of biomarkers. The correlations described in the methods of the claims are simpler than the ones described in Wacholder and thus would not require the testing of hundreds of subjects. Second, the methods of the invention do not require that a correlation that works for most or many subjects be found. The pending claims are drawn to a method of identifying a substance that is likely to prevent or diminish a biological response in a subject, not necessarily in many subjects. While a correlation demonstrated in only one subject may not be meaningful for every other possible subject, the correlation should be meaningful for the subject tested. For these reasons, Applicants submit that the teachings of Wacholder do not suggest that the claimed invention requires experimentation in order to be practiced.

Unpredictability of the Art and the State of the Prior Art

The Examiner asserted, on page 7 of the Office Action, that the specific alleles claimed are not associated with particular inflammatory diseases. Thus, the Examiner reasoned that it would be unpredictable which allele is associated with which disease and which biomarker would function as a surrogate for that allele. Further, the Examiner alleged that the specification only provided support for the association of five alleles with various diseases.

The Examiner cited Bajnok *et al.* Bone 27(4):559-562 (2000) ("Bajnok"), Riggio *et al.* . Clin. Periodontol. 28:430-436 (2001) ("Riggio"), Tsai *et al.* Neuroscience Letters 343:93-96 (2003) ("Tsai"), Donn *et al.* Rheumatology 38(2):171-175 (1999) ("Donn"), Gonzalez *et al.* Eur. J. Oral Sci. 111:395-399 (2003) ("Gonzales") Maruculescu *et al.* Thromb. Haemost. 94:646-650

⁷ See Wacholder at page 434, column 1.

⁸ *Id.*

(2005) ("Maruculescu"), Volzke *et al.* Clinical Science 106:35-42 (2004) ("Volzke"), Nishibu *et al.* J. Dermatol. Science 29:181-184 (2002) ("Nishibu") Louis *et al.* Eur. Respir. J. 16:604-608 (2000) ("Louis"), Moller *et al.* Neuroscience Letters 359:195-197 (2004) ("Moller"), and Muhlberg *et al.* European J. Endocrinol. 138: 686-690 (1998) ("Muhlberg") to suggest that none of the genes listed in the pending claims are linked to any inflammatory disease. The Examiner also cited Lucentini *et al.* The Scientist Vol. 18 (2004) ("Lucentini"), Wacholder and Ioannidis Nature Genetics 29:306-309 (2001) ("Ioannidis") to suggest that single alleles are not able to be reliably linked to disease states. Thus, the Examiner argued that the alleles of the instant claims cannot be predictably linked to a disease state and thus the screening methods of the invention cannot produce meaningful results. Applicants respectfully disagree.

The references that the Examiner cites teaching that a specific pathology is not linked with a particular allele of the instant claims, all teach that the genes and associated alleles are correlated with inflammatory diseases, generally.⁹ Thus, the references cited by the Examiner all teach that one of ordinary skill in the art would expect the claimed alleles to be associated with inflammatory diseases.

The three references that the Examiner cited regarding the invalidity of correlation of alleles to disease states are not relevant to the invention of the instant claims. Ioannidis, Wacholder and Lucentini all teach about the lack of predictability between correlations between alleles and disease states, not between alleles and inflammatory disease related phenotypes of biomarkers. As explained above, a disease state may comprise a number of phenotypic states, making their analysis more complicated. The claims as pending are not drawn to the screening of substances based on a correlation between any allele and a disease state, but 21 specific alleles and the phenotype of biomarkers. Ioannidis, Wacholder and Lucentini do not specifically teach anything regarding these sorts of correlations. However, because of the greater simplicity involved, one of ordinary skill in the art would expect greater success with the methods of the invention than the authors of the above references showed.

⁹ See Bajnok at page 559, column 2, first full paragraph, Riggio at page 430, second columns 2-3, Tsai at page 93, columns 1 and 2, Donn at page 171 column 2, last paragraph, Gonzales at page 395, column 1, Marcelscu at page 646, lines 2-4 of the Summary, Volzke at page 36, second full paragraph, Nishibu at page 181, lines 1-2 of the Abstract, Louis at page 604, lines 1-2 of the Abstract, Moller at page 195, first column, and Muhlberg at page 686, first column.

Working Examples.

The Examiner asserted that the specification gives no working examples of the methods of the invention, in that the specification does not specifically set out what the association of the biomarkers with any of the specific polymorphisms claimed would be.

Applicants submit that the specification gives specific teachings on how to practice the invention. Suggested biomarkers are found in Table 2 on pages 27-28 of the instant specification. Specific inducers are found in Table 3 on pages 29 and 30 of the instant specification. Specific methods on how to genotype subjects are found in Example 6.1 on pages 33-39 of the instant specification. Thus, Applicants submit that the instant specification does provide working examples.

Guidance in the Specification

The Examiner alleged, on page 12 of the Office Action, that the specification provides no guidance on how to resolve the contradictions in the prior art regarding the lack of association of the alleles and any specific inflammatory disease. Further, that the specification does not teach which biomarkers are associated with which alleles or which combination of disease, allele and biomarker are correlated with each other.

Applicants fail to see the relevance of the Examiner's assertions. The methods are directed to methods of screening for correlations between a subject with a specific genotype treated with a specific compound and the effect this combination has on a inflammatory disease associated phenotype of a biomarker. If the information the Examiner alleges is missing from the specification existed in its totality, there would be no need to use a screening method to create this information. Further, Applicants remind the Examiner that the claims do not mention nor are they drawn to the correlation of a disease with a genotype, biomarker or compound. An inflammatory disease associated phenotype of a biomarker is correlated with genotype and presence of a compound. The subject may not have any disease but still have a biomarker with a disease mediated phenotype.

Level of Skill in the Art

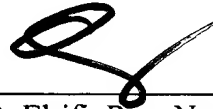
The level of skill in the art is deemed to be high.

In light of the above Wands factor analysis, Applicants submit that the instant claims are enabled and request that this rejection be withdrawn.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance, and a Notice of Allowance is respectfully requested. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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